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# Estimating the Cost-Effectiveness of Fluticasone Propionate for Treating Chronic Obstructive Pulmonary Disease in the Presence of Missing Data

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## ABSTRACT

**Objectives:** To explore the cost-effectiveness of fluticasone propionate (FP) for the treatment of chronic obstructive pulmonary disease (COPD), we estimated costs and quality-adjusted life-years (QALYs) over 3 years, based on an economic appraisal of a previously reported clinical trial (Inhaled Steroids in Obstructive Lung Disease in Europe [ISOLDE]).

**Methods:** Seven hundred forty-two patients enrolled in the ISOLDE trial who received either FP or placebo had data available on health-care costs and quality of life over the period of the study. The SF-36-based utility scores for quality of life were used to calculate QALYs. A combined imputation and bootstrapping procedure was employed to handle missing data and to estimate statistical uncertainty in the estimated cumulative costs and QALYs over the study period. The imputation approach was based on propensity scoring and nesting this approach within the bootstrap ensured that multiple imputations were performed such that statistical estimates included imputation uncertainty.

**Results:** Complete data were available on mortality within the follow-up period of the study and a nonsignificant trend toward improved survival of 0.06 (95% confidence interval [CI] -0.01 to 0.15) life-years was observed. In an analysis based on a propensity scoring approach to missing data we estimated the incremental costs of FP versus placebo to be

£1021 (95% CI £619–1338) with an additional effect of 0.11 QALYs (CI 0.04–0.20). Cost-effectiveness estimates for the within-trial period of £17,700 per life-year gained (£6900 to ∞) and £9500 per QALY gained (CI £4300–26,500) were generated that include uncertainty due to the imputation process. An alternative imputation approach did not materially affect these estimates.

**Conclusions:** Previous analyses of the ISOLDE study showed significant improvement on disease-specific health status measures and a trend toward a survival advantage for treatment with FP. This analysis shows that joint considerations of quality of life and survival result in a substantial increase in QALYs favoring treatment with FP. Based on these data, the inhaled corticosteroid FP appears cost-effective for the treatment of COPD. Confirmation or refutation of this result may be achieved once the Towards a Revolution in COPD Health (TORCH) study reports, a large randomized controlled trial powered to detect mortality changes associated with the use of FP alone, or in combination with salmeterol, which is also collecting resource use and utility data suitable for estimating cost-effectiveness.

## Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as a chronic disease characterized by nonreversible airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lungs to particles and gases, and particularly tobacco smoke [1]. The symptoms of COPD, resulting from airway irritation and altered

lung function, include coughing, sputum production, breathlessness, wheezing, and chest pain [1]. In addition to chronic symptoms, subjects with COPD may also experience episodes of acute exacerbations, commonly triggered by respiratory infection [1] that frequently require intense medical follow-up in hospital, sometimes including respiratory therapy [2]. The impact of COPD on health-related quality of life is well-documented; worse health is associated with an increased likelihood of hospitalization [3], more frequent exacerbations [4], and increased mortality [5]. A recent study has shown that frequent exacerbations are associated with a more rapid decline in health status [6].

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With an approximate global prevalence of 600 million and 2.5 million deaths recorded worldwide annually, COPD was estimated to be the eleventh leading cause of disability and the fifth leading cause of mortality in 2000 [7]. Because of aging populations, air pollution [8], and rapid increases in the rate of cigarette smoking in some (mostly developing) countries [9–13] and among specific subgroups [14], it is projected that, by 2020, COPD will become the fifth leading cause of disability and third leading cause of death in the world [15].

Available treatments for moderate to severe COPD mostly comprise single agent or combination bronchodilator therapy (i.e., short or long acting  $\beta_2$ -agonists, inhaled anticholinergics and theophyllines), and oral corticosteroids to manage COPD exacerbations [16,17]. Few long-term studies have investigated the effect of inhaled corticosteroids on lung function and exacerbations. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study was a randomized, placebo-controlled clinical trial comparing inhaled fluticasone propionate (FP) versus placebo in 751 subjects with moderate to severe COPD [18,19]. The objective was to determine the effect of treatment on lung function, exacerbations, and health status over the 3-year follow-up of the trial. The results showed that, although FP did not reduce the annual rate of decline in lung function compared with placebo, significant benefits were achieved in terms of reduced frequency of exacerbations and a reduction in the decline of health status [18,19]. Because of their strong association with prolonged hospitalization and death [4], COPD exacerbations are often interpreted as a pertinent health outcome. In that regard, the ISOLDE study showed that inhaled corticosteroids could potentially yield important benefits.

Although a main focus of the original clinical trial was deterioration of health status as measured by the disease-specific St George's Respiratory Questionnaire (SGRQ) [20], the generic SF-36 health status measure was also included in ISOLDE [21]. The reduction in rate of health status deterioration associated with FP treatment occurred over all domains of the SGRQ and the Physical Function, Physical Role, Energy/Vitality, and Mental Health domains of the SF-36 [21]. The recent publication of an algorithm to translate SF-36 scores into utility scores [22] offers, for the first time, the potential for the improvement in health status associated with treatment already observed in ISOLDE to be translated into a gain in quality-adjusted life-years (QALYs). QALYs explicitly combine length and quality of life in a single measure and are the preferred metric in health economic evaluations for bodies such as the National Institute for Clinical Excellence (NICE) in the UK [23], because they allow the direct comparison of treatment cost-effectiveness between disease areas. The aim of the present study is to assess

the cost-effectiveness of FP for the treatment of COPD, by performing an economic evaluation of the ISOLDE trial data, estimating costs and QALYs over the 3-year follow-up of the trial.

## Methods

After the early withdrawal of nine patients before double-blind randomization in the ISOLDE trial, 742 patients were available for analysis. The economic analysis was conducted from a UK public sector (Health and Personal Social Services) perspective over the 3 years of the clinical study. When reporting cost-effectiveness results costs and effects were discounted at the rate of 3.5% per annum, the rate currently recommended in the most recent guidance from NICE in the UK [23].

### *Calculation of Utility Scores*

In the ISOLDE study, the generic SF-36 instrument was administered at baseline and every 6 months for the 3 years of follow-up, generating a maximum of seven possible observations for each patient enrolled in the trial. Brazier and colleagues have reported work on deriving a reduced health status index from the SF-36 that they term the SF-6D [24] and more recently, they have published an algorithm that allows the estimation of utility scores for all states of the SF-6D index [22]. Following this published algorithm, the SF-36 scores observed in the trial were converted to utility scores. QALYs were calculated assuming linear interpolation between each observed 6-month visit [25] and calculating the area under the curve to give a QALY score per patient over the trial period. The mean QALY difference was adjusted for a slight (nonsignificant) difference between the baseline utility scores between the two arms [26], which has been shown to be important for the unbiased assessment of mean QALY differences [27].

### *Estimation of Costs*

In addition to the cost of treatment, six categories of resource were collected as part of ISOLDE: rescue medication use, concomitant medication use, visits to the general practitioner, visits to outpatient clinics, visits to the emergency room, and inpatient hospital stays. Unit costs for medications were obtained from the British National Formulary (comparison of the contemporary price of FP shows that it remains at the same cost as the base year of this study [28]), and the unit costs of health service contacts from a published compendium of unit cost figures [29]. For the purposes of this analysis, costs were accrued for the same 6-month periods relating to the visits at which health status was measured. Accumulating these costs over the maximum six periods (3 years) gave the per-patient total cost for the study. The costing employs a

base year of 1998 to 1999, corresponding to the year in which trial ended.

### Missing Data Due to Attrition

One important issue observed in the ISOLDE clinical trial was the high rate of withdrawals over the 3 years of follow-up. Experiencing COPD-related adverse events was also stated as one of the main reasons for dropping out and the overall rate of dropout was higher in the placebo group at 53% of subjects compared with 43% in the FP group [20]. Consequently, a large amount of data on periodic costs and utilities had missing values over the 3 years of the clinical study, which prevented the total cost and QALY scores being calculated for these patients. Although the original clinical study reported 36 deaths during the study period in the placebo group compared with 32 among those allocated to FP, these represented only deaths before dropout from the study. Retrospective examination of death records revealed that there were in fact 58 deaths among those allocated placebo within the 3-year period of the study compared with just 45 in the FP arm of the study. Having adjusted for data known to be unavailable as a result of death, the rate of missing data observations was estimated to be 20% for costs and 34% for SF-36 information at scheduled visit dates (Table 1).

A preliminary analysis of QALYs and cost, including a breakdown of costs by resource use category, was conducted based only on the complete cases (complete information was available for the life-year analysis as described above). This provides a useful reference point for comparison with the full imputation analysis described below. When combining complete cases of cost and QALYs (and life-years) to estimate cost-effectiveness the full set of complete case information for each component of the calculation was retained. That is, cost data were not dropped if the patient did not have a complete utility score and vice versa. Nevertheless, covariance information for confidence interval (CI) calculation could only be estimated from patients that had both cost and effect information available.

### Imputation of Missing Information

For cost and utility information that was missing after dropout from the study, but before death/end of the 3-year follow-up period, the values of the missing observations were imputed. Following Oostenbrink and colleagues [30], an imputation approach based on propensity scoring was employed with baseline variables including age, smoking status, sex, pulmonary function (forced expiratory volume in 1 s), body mass index categories, and disease-specific SGRQ score, entered into a logistic regression to predict the chance of a missing value. In addition, one-period-lagged values of the relevant cost or utility score were included as explanatory variables. To avoid missing lagged values, the imputation equations were fitted sequentially and imputed lagged values were used where appropriate. The predicted probability from this regression is the propensity score and on the basis of this predicted probability, the available data were arranged into quintiles. Where cost data or a utility score were missing, a replacement value was selected at random from the available data points within the same quintile. By choosing a value at random within the same quintile the principle of multiple imputation could be employed [31]. Multiple imputation procedures are considered more valid than single imputation methods because instead of filling in a single value and treating it as known, as would be the case if a single value based on the closest propensity match was used, in each imputation uncertainty in the imputation process is taken into account such that the imputed data points represent a random sample of the missing values [32].

Although the standard approach is to use a small number of imputed data sets in a multiple imputation process, the recent International Society for Pharmacoeconomics and Outcomes Research Task Force on cost-effectiveness analysis alongside clinical trials suggested that both statistical and imputation uncertainty could be combined by bootstrapping the whole imputation/estimation process [33]. Therefore, the existing data set was first bootstrapped including the missing data and then the imputation process was employed to fill in the missing values. The whole bootstrap/

**Table 1** Missing data observations and implications for complete cases

	Quality of life utility		Total costs	
	Placebo (n = 370)	FP (n = 372)	Placebo (n = 370)	FP (n = 372)
Maximum number of observations	2220	2232	2220	2232
Total observations*	2077	2129	2077	2129
Of which complete	1279	1459	1616	1749
% observations missing	38	31	22	19
Total cases complete	121	154	242	269
% cases missing	67	59	35	28

\*Total observations are less than maximum number of observations because of deaths within the study period and do not include the baseline assessment of utility.

FP, fluticasone propionate.

imputation procedure was then repeated 1000 times to generate an overall estimate of uncertainty that includes uncertainty in the imputation process.

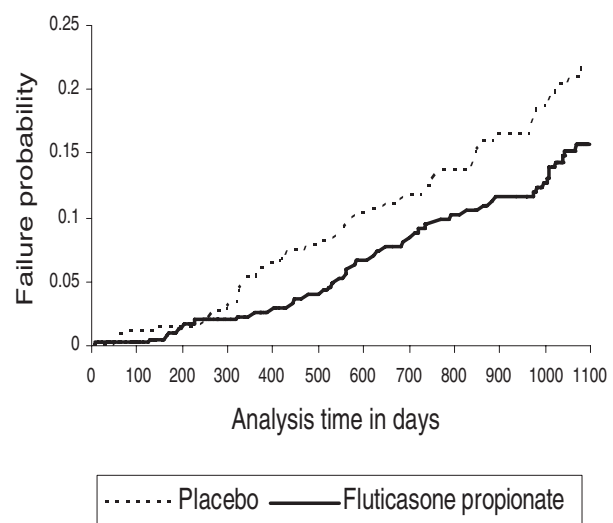
In a more qualitative sensitivity analysis of the imputation procedure, a best and worst case analysis was also performed. For the best case, imputed values for the costs and utilities in the FP group were based on the mean cost and utility in the first period for all completers, and for the placebo group the mean cost and utility in the last available period for subjects that eventually dropped out, when costs were generally higher and utilities lower. For the worst case scenario, we applied the reverse logic by imputing values for FP that were based on mean cost and utility for the last period before subjects dropping out and for the placebo group we used the mean costs and utility in the first period for all completers. This alternative imputation approach allowed the importance of the chosen imputation method to be assessed and in particular allows the assessment of the sensitivity of the results to the possibly nonignorable nature of the missing data.

### Economic Analysis

The three outcomes estimated for the economic analysis were cumulative costs, life expectancy, and quality-adjusted life expectancy over 3 years. To determine cost-effectiveness, we calculated the incremental cost-effectiveness ratio (ICER) as the ratio of the difference in costs between FP and placebo to the difference in effects. Lower values of the ratio suggest that the benefits of treatment come at lower cost and therefore indicate better value for money. Both the nonparametric bootstrap and Fieller's theorem [34,35] were employed to generate CIs for cost-effectiveness estimates based on complete data, whereas just the nonparametric bootstrap was used to represent the combination of statistical/imputation uncertainty where multiple imputation was employed. Uncertainty surrounding the ICER was also presented on the cost-effectiveness plane [36,37].

### Results

The mortality curves for FP and placebo are presented in Figure 1. The difference in survival was estimated to be 23 days or 0.06 life-years over the study period, although this difference did not reach statistical significance at conventional levels ( $P = 0.11$ ). No imputation was necessary for mortality because the data were complete. The extent of missing information relating to cost and utility is summarized in Table 1 and shows that approximately 20% of the observations relating to cost and 34% of the observations relating to utility were missing. Furthermore, data were more likely to be missing from the placebo than the treatment group. These missing observations have a more profound effect on complete cases with just 69% of patients hav-

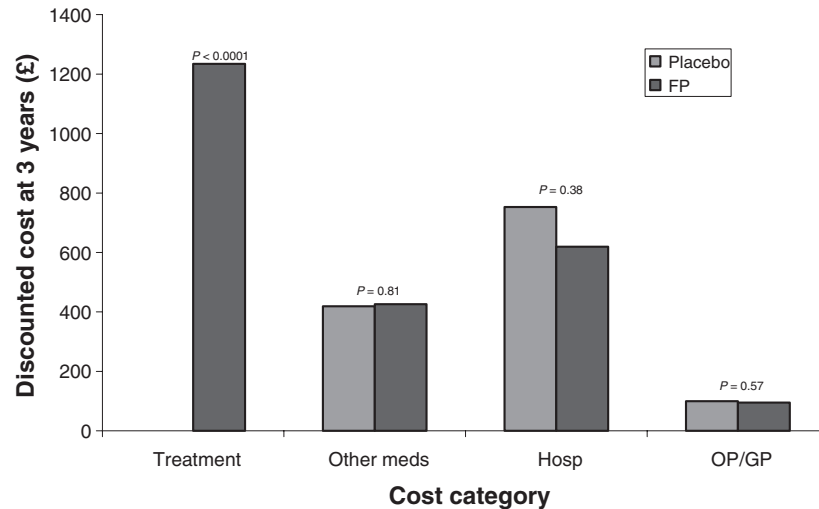


**Figure 1** Failure curves for time to death in the placebo and fluticasone propionate (FP) arms. Separation shown is nonsignificant ( $P = 0.11$ ).

ing a complete set of cost data and only 37% of patients having complete information on utilities. The breakdown of costs into treatment costs, other medication use, primary care contacts and secondary care visits is shown in Figure 2 by treatment allocation. This shows clearly that the additional costs of FP are only partially offset by a (nonsignificant) reduction in hospitalization costs with no apparent effect on other categories of cost.

A complete case analysis based only on those patients that had full and complete data for the 3-year follow-up of the study is reported in Table 2, with all CIs based on the nonparametric bootstrap; parametric intervals based on Fieller's method produced very similar outcomes. These results show that FP is associated with a significantly increased cost, but also a benefit in terms of QALYs gained (bordering on statistical significance) over the 3-year study period. These results are presented on the cost-effectiveness plane in terms of both life-years and QALYs gained in Figure 3, where the close correspondence between the bootstrap and the assumption of multivariate normality of the joint density of costs and effects is apparent. Despite these promising results there are two concerns with the complete case analysis presented in Table 2 and Figure 3. First, the reduced sample size as a basis for this analysis is wasteful of information, because of excluding patients with some information, but who are missing at least one data point, with consequent loss of power. Second, the results may be biased if the data are not missing completely at random.

The imputation results for the propensity scoring method are reported in Table 3 and Figure 4 where CIs are now calculated nonparametrically and include both sampling and imputation uncertainty by nesting the imputation within the bootstrap. The incremental



**Figure 2** Costs split by treatment group for placebo and control arms (based on complete cases). Treatment, costs of study medication; Other meds, all other medications costs; Hosp, costs of inpatient and emergency department visits; OP/GP, costs of visits to outpatient departments or primary care physicians. P-values shown are for standard t-tests for difference between treatment groups for each category.

costs of FP versus placebo was estimated to be £1021 (95% CI £619–1338) with an additional effect of 0.11 QALYs (0.04–0.20). The discounted cost-effectiveness for the within-trial period was estimated to be £17,700 per life-year gained (£6900 to ∞) and £9500 per QALY gained (£4300–26,500). The results of the sensitivity analysis for the best case scenario resulted in an ICER point estimate of £5200 whereas the worst case scenario yielded an ICER of £13,200.

The confidence ellipses of Figure 2 (Fieller's method assumptions) based on complete case analysis are over-

laid in Figure 4 and show how the imputation approach changes the location of the joint distribution slightly, but that the main effect is to reduce the variance of the estimates, particularly for QALYs gained where missing data observations were greatest.

## Discussion

In this study, we have estimated the cost-effectiveness of FP versus placebo using data from the previously published ISOLDE study. It is only after the publica-

**Table 2** Cost effectiveness analysis based only on complete cases

	N	Placebo (95% CI)	N	FP (95% CI)	Difference (95% CI)
Life-years	370	2.75 (2.68–2.80)	372	2.81 (2.76–2.86)	0.06 (–0.01–0.14)
QALYs	121	1.74 (1.62–1.84)	154	1.88 (1.79–1.97)	0.12* (–0.00–0.25)
Cost	242	£1341 (£1110–£1600)	269	£2494 (£2274–£2715)	£1,153 (£820–£1472)
Cost per life-year (£)					
Undiscounted					18,400 (7500–∞)
Discounted					20,000 (8100–∞)
Cost per QALY (£)					
Undiscounted					9,500 (4300–∞)
Discounted					9,600 (4400–∞)

\*After controlling for baseline utility.

CI, confidence interval; FP, fluticasone propionate; QALY, quality-adjusted life-year.

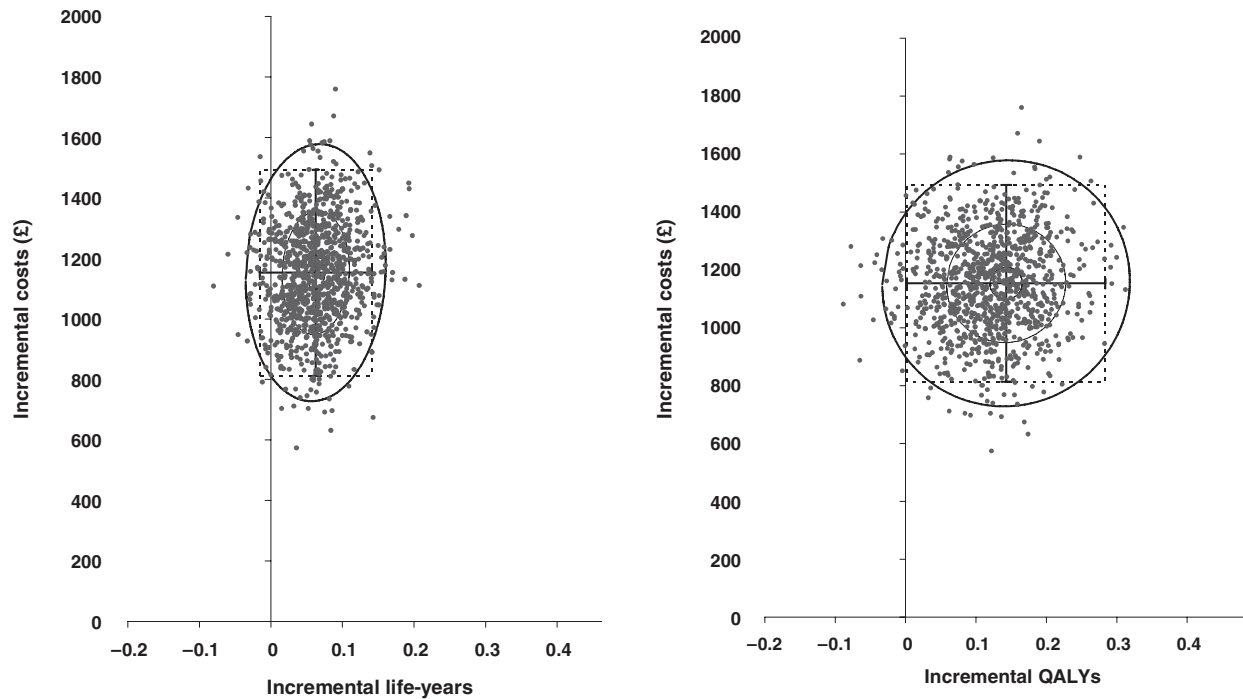
**Table 3** Cost-effectiveness analysis based on full imputation

	N	Placebo (95% CI)	N	FP (95% CI)	Difference (95% CI)
Life-years	370	2.74 (2.68–2.80)	372	2.81 (2.76–2.85)	0.06 (–0.01–0.14)
QALYs	370	1.74 (1.67–1.80)	372	1.86 (1.82–1.93)	0.11* (0.04–0.20)
Cost	370	£1509 (£1286–£1879)	372	£2530 (£2341–£2774)	£1,021 (£619–£1338)
Cost per life-year (£)					
Undiscounted					£16,300 (£6400–∞)
Discounted					£17,700 (£6900–∞)
Cost per QALY (£)					
Undiscounted					£9,600 (£4200–£26,500)
Discounted					£9,500 (£4300–£26,500)

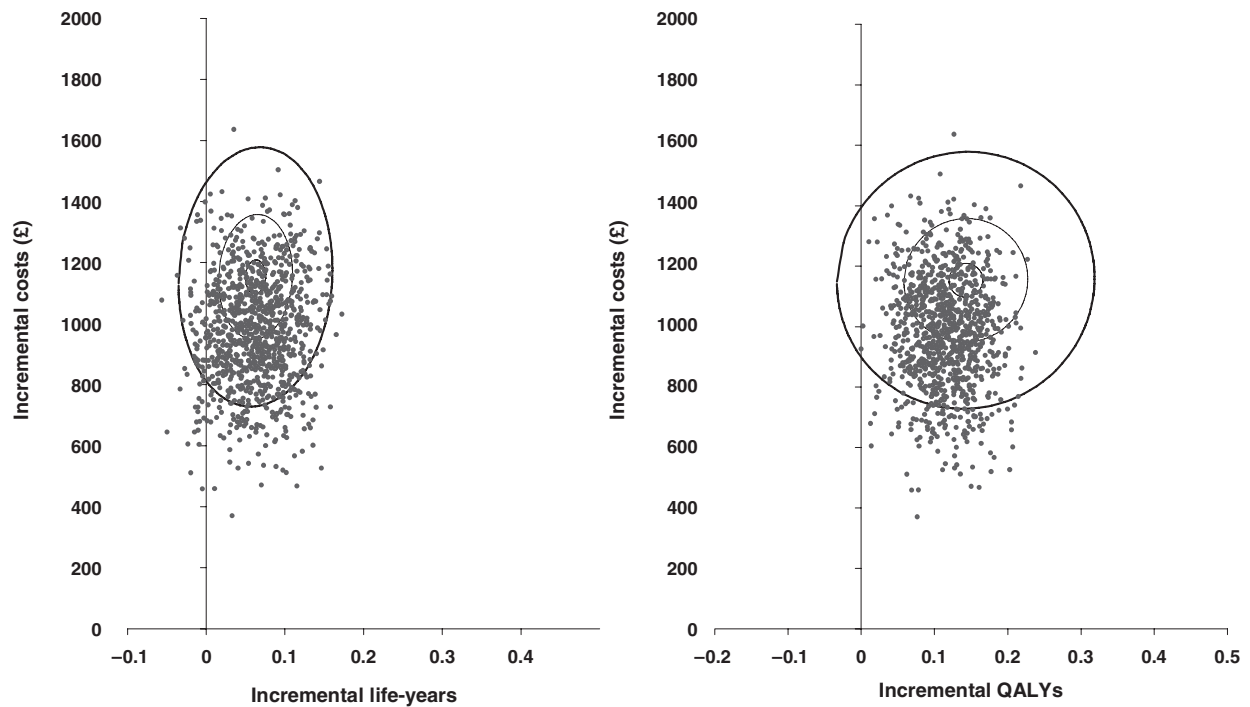
\*After controlling for baseline utility.

CI, confidence interval; FP, fluticasone propionate; QALY, quality-adjusted life-year.





**Figure 3** Complete case cost-effectiveness on the cost-effectiveness plane: left panel shows cost per life-year; right panel shows cost per quality-adjusted life-year (QALY). Bars show 95% confidence intervals for incremental cost and effect crossing at the point estimates; joint distribution of incremental cost and effect is shown using 5%, 50%, and 95% confidence ellipses.



**Figure 4** Full imputed cost-effectiveness analysis on the cost-effectiveness plane: left panel shows cost per life-year; right panel shows cost per quality-adjusted life-year (QALY). Imputed results are shown by the bootstrap joint densities; ellipses based on complete case analysis of Figure 2 overlaid for comparison.

tion of an algorithm for converting data on the SF-36 instrument to utility scores suitable for calculating QALYs that it has been possible to directly estimate cost-utility results from ISOLDE. ISOLDE was not designed to have sufficient power to detect differences between groups for mortality, but nevertheless showed a trend toward reduced mortality. The results of the analysis reported here show that combining that trend with the significant improvement previously reported in health status resulted in a highly significant QALY gain. Nevertheless, given the retrospective nature of the analysis and the fact that the study was not powered for mortality differences, these results should be considered as hypothesis generating.

The high rate of withdrawal in the clinical study required the use of imputation techniques to handle missing data. Of particular concern was that there was a strong indication that the attrition was related to adverse outcomes with those experiencing COPD-related adverse events representing the majority of patients dropping out of the study. This means that the underlying pattern of missingness was certainly not completely at random and may be informative. Informative missingness is problematic in that any use of statistical techniques based on observed data are potentially misleading, and modeling unobserved data requires assumptions that are difficult to verify. Our solution was to use propensity scoring as the base case analysis, because this at least imputes from the group of patients that had a similar propensity to have missing values and might therefore account for some of the informative nature of those missing values. In addition, a more qualitative analysis of replacing missing values examined “best case” and “worst case” scenarios, from the perspective of the intervention under study, and revealed that even if missing values were deliberately stacked against the intervention, the estimate of cost-effectiveness was still within acceptable limits. That the estimated cost-effectiveness was insensitive to the choice of imputation method used (even under extreme assumptions) suggests that the level of missingness in ISOLDE does not invalidate the results.

The comparison between the complete case analysis and the imputation analysis raises a number of interesting issues. It is quite clear that the main impact of using the imputed data has been to reduce the variance—this is due to the fact that many more data points are now being used in the analysis with consequent increase in precision of estimation. The effect on the point estimates is less remarkable. There was a slight reduction in both the point estimate of the cost difference and the incremental QALY gain following imputation, which had little impact on the estimated cost-effectiveness ratio. Under an assumption that missing values are nonignorable and quality of life outcomes are worse for those dropping out, it would be reasonable to expect that the QALY gain would

increase following imputation (due to the lower attrition rate in the FP arm), but this was not the direction of the effect that was observed, although given the overall uncertainty we are reluctant to read too much into this. Nevertheless, the propensity scoring approach is only really valid for MAR patterns of missingness. Although a number of authors have suggested methods for handling missingness that would attempt to impute observations based on the assumption that missing values are nonignorable [38], formal testing of those assumptions is difficult in a statistical sense. Although potentially open to criticism, the MAR assumption in this case is most likely to bias against the true cost-effectiveness of FP, because any assumption of poorer outcomes among missing observations would accentuate the difference between the arms because of the differential dropout.

The original costing of ISOLDE was undertaken using a cost base year corresponding to the year that the trial closed. Although this may seem to be out of date for a current analysis, we have not attempted to update the costing for two main reasons. First, for some resource use categories (such as concomitant medications) the individual resource use quantities are not available, and so any updating of costs could only be achieved through the use of a health service inflation index. Second, the price of FP has not changed since the trial was undertaken. Therefore, the analysis presented here is conservative, because the cost of FP is effectively the current price, and any cost-savings from the reduction in other health service resource use associated with treatment are currently valued using 1998/99 unit costs.

The results of this study suggest that inhaled FP is associated with increased quality-adjusted survival when compared with placebo. This adds support to the need to account for the quality-of-life considerations when evaluating treatments for COPD. These benefits came at relatively small overall incremental costs resulting in a favorable cost-effectiveness ratio for FP compared with placebo. For example, although NICE have strenuously denied the existence of a single cost-per-QALY threshold, they have indicated that they would be unlikely to reject a treatment in the range from £5000 to £15,000 per QALY purely on cost-effectiveness grounds [39]. The effect of inhaled corticosteroids alone or in combination with a long acting beta-agonist on survival is currently being investigated in TORCH (TOwards a Revolution in COPD Health), a large randomized controlled trial involving more than 6000 patients comparing the effects of FP alone, or in combination with salmeterol, with placebo [40]. This study should provide further evidence on the effectiveness and cost-effectiveness of inhaled corticosteroids alone and in combination and could provide the definitive analysis to confirm or refute the ISOLDE results presented here.



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